Crystal structure and n.m.r. analysis of lactulose trihydrate

ABSTRACT

The ^{13}C CPMAS n.m.r. spectrum of 4-*O*-β-D-galactopyranosyl-D-fructose (lactulose) trihydrate, $C_{12}H_{22}O_{11}\cdot 3\ H_2O$, identifies the isomer in the crystals as the β-furanose. This is confirmed by a crystal structure analysis, using Cu$K\alpha$ X-ray data at room temperature. The space group is $P2_12_12_1$, with $Z = 4$ and cell dimensions $a = 9.6251(3)$, $b = 12.8096(3)$, $c = 17.7563(4)$ Å. The structure was refined to $R = 0.031$ and R_w 0.025 for 1929 observed structure amplitudes. All the hydrogen atoms were unambigously located on difference syntheses. The conformation of the pyranose ring is the normal $^4C_1$ chair and that of the furanose ring is $^4T_3$. The 1→4 linkage torsion angles are O-5′–C-1′–O-1′–C-4 = −79.9(2)° and C-1′–O-1′–C-4–C-5 = −170.3(2)°. All hydroxyls, ring and glycosidic oxygens, and water molecules are involved in the hydrogen bonding, which consists of infinite chains linked together by water molecules to form a three-dimensional network. There is a three-centered intramolecular, interresidue hydrogen bond from O-3-H to O-5′ and O-6′. The n.m.r. spectrum of the amorphous, dehydrated trihydrate suggests the occurence of a solid-state reaction forming the same isomeric mixture as was observed in crystalline anhydrous lactulose, although the mutarotation of the trihydrate when dissolved in Me_2SO is very slow.

INTRODUCTION

Crystalline lactulose is normally anhydrous and is a mixture of three isomers, which differ in the form of their reducing fructose residues. A combined solid-state n.m.r. and crystal-structure analysis[1] showed the presence of β-furanose, α-furanose, and β-pyranose in the ratio of 75:10:15. Such complex mixtures in the same crystal are rarely observed. In carbohydrates, isomeric mixing in the solid state is generally confined to α and β anomers having the same ring conformation[2]. This study was undertaken to examine molecular content, conformation, and hydrogen bonding in the crystals of the trihydrate.

Crystallization. — Crystals of lactulose trihydrate were obtained from a 70% aq. solution of lactulose (Merck, Darmstadt) that was kept at 4° for several months. More crystals were obtained by using these initial trihydrate crystals to seed a solution prepared by dissolving 245 g of anhydrous lactulose in 105 g of water with gentle warming, then cooling to room temperature.

Solid state n.m.r. — Carbon-13 CPMAS spectra were obtained on a Bruker MSL-300 NMR spectrometer operating at 75.46 MHz. Chemical shifts were measured relative to the upfield peak of adamantane, taken as 29.50 p.p.m. Samples were examined in a 5 mm ZrO_2 rotor spinning at 3.0 kHz. Contact times of 1.0 ms were used with 2.5 s repetition times and 12 G ^1H decoupling. Spectral width was 18 500 Hz, with 1024 data points zero-filled to 2048 points. To identify resonances representing non-protonated carbons, interrupted proton decoupled (IPD) spectra were obtained by the insertion of a delay of 50 μs following the contact time[3].

Solution state n.m.r. — The 75.46 MHz ^{13}C spectra were recorded on a Bruker MSL-300 n.m.r. spectrometer equipped with a 5 mm probe. Each 40 mg sample was dissolved in dry Me_2SO-d_6 and the spectrum was run immediately. All shifts were measured relative to the CH_3 of Me_2SO at 39.5 p.p.m. The spectra were produced from 256 scans (90° pulses) with 3 s repetition times to insure complete relaxation. Spectral widths were 15 000 Hz, with 8 K data points. The time course of mutarotation was followed in a stacked experiment with delay times of 60 min between consecutive spectra.

Crystal structure analysis. — The X-ray diffraction data are given in Table I. The crystal structure was determined using the direct-method program MITHRIL[4]. All hydrogen atoms were located on difference maps. A full-matrix least-squares refinement was carried out using the program UPALS[5], with anisotropic thermal parameters for

TABLE I

Crystal data and structure determination and refinement data for lactulose trihydrate

Crystal data

$C_{12}H_{22}O_{11} \cdot 3\ H_2O$, mol. wt. 396.3, m.p. 68.1°, $P2_12_12_1$, $Z = 4$
Cell dimensions at 295 K: $a = 9.6251(3)$, $b = 12.8096(3)$, $c = 14.7563(4)$ Å
$V = 1819.4$ Å^3, $D_x = 1.447$ g cm^{-3}, $F000 = 848$

Structure determination and refinement data

Crystal dimensions 0.26 × 0.17 × 0.16 mm
Radiation: Cu$K\alpha$ ($\lambda = 1.5418$ Å), Ni-filtered, μ(Cu$K\alpha$) = 11.87 cm^{-1}
Absorption correction: max. 1.203 cm^{-1}, min. 1.143 cm^{-1}
2035 intensities measured on a CAD-4 diffractometer with Rigaku RU100 rotating anode generator; 1929 intensities with $I \geq 2\sigma(I)$
2θ limits: $2° \leq 2\theta \leq 72°$
319 parameters; refinement using UPALS[5], minimizing $w(k|F_o| - |F_c|)^2$, where $w = 1/\sigma^2(F)$
Final agreement factors: $R(F) = 0.031$, $R_w(F) = 0.025$

TABLE II. Positional parameters and equivalent isotropic thermal parameters for lactulose trihydrate[a]

Atom	x/a	y/b	z/c	B_{eq} ($Å^2$)
C-1	1250(3) × 10^{-4}	11563(2) × 10^{-4}	6735(2) × 10^{-4}	239(7) × 10^{-2}
C-2	1927(3)	10726(2)	7308(2)	195(6)
C-3	2264(3)	9711(2)	6797(2)	201(6)
C-4	2134(3)	8884(2)	7531(2)	181(6)
C-5	887(3)	9280(2)	8048(2)	177(6)
C-6	804(3)	8916(2)	9011(2)	227(6)
C-1′	2883(3)	7276(2)	6869(2)	159(6)
C-2′	2450(3)	6130(2)	6887(2)	155(6)
C-3′	3507(3)	5474(2)	6367(2)	174(6)
C-4′	3762(3)	5909(2)	5417(2)	196(6)
C-5′	4152(3)	7060(2)	5498(2)	179(6)
C-6′	4361(3)	7589(2)	4600(2)	248(7)
O-1	31(3)	11165(2)	6314(1)	288(5)
O-2	3142(2)	11115(2)	7715(2)	276(5)
O-3	3567(3)	9795(2)	6364(2)	354(6)
O-5	955(2)	10406(1)	7998(1)	220(4)
O-6	− 518(3)	9201(2)	9366(1)	321(6)
O-1′	1798(2)	7852(1)	7238(1)	177(4)
O-2′	2388(2)	5746(2)	7789(1)	209(5)
O-3′	3105(2)	4400(2)	6349(1)	222(5)
O-4′	2628(2)	5749(2)	4816(1)	247(5)
O-5′	3053(2)	7615(1)	5953(1)	176(4)
O-6′	4847(3)	8626(2)	4773(1)	301(6)
O-W-1	6867(4)	8264(2)	6973(2)	449(8)
O-W-2	4514(2)	6353(2)	8877(1)	290(6)
O-W-3	4742(3)	8379(2)	9537(2)	460(8)
H-1	100(3) × 10^{-3}	1218(2) × 10^{-3}	713(2) × 10^{-3}	
H′-1	190(3)	1186(2)	628(2)	
H-3	150(3)	959(2)	639(2)	
H-4	295(3)	886(2)	791(2)	
H-5	12(2)	911(2)	775(1)	
H-6	162(2)	928(2)	938(2)	
H′-6	99(3)	808(2)	903(2)	
H-1′	381(3)	741(2)	724(2)	
H-2′	151(3)	604(2)	661(2)	
H-3′	442(3)	552(2)	662(2)	
H-4′	449(3)	549(2)	515(2)	
H-5′	499(2)	713(2)	585(1)	
H-6′	346(3)	756(2)	423(2)	
H′-6′	516(3)	719(2)	426(2)	
H-O-1	1(4)	1127(3)	588(2)	
H-O-2	304(3)	1177(2)	775(2)	
H-O-3	364(3)	936(2)	607(2)	
H-O-6	− 53(3)	911(2)	982(2)	
H-O-2′	177(3)	587(2)	793(2)	
H-O-3′	243(3)	435(2)	614(2)	
H-O-4′	203(3)	596(2)	493(2)	
H-O-6′	463(3)	897(2)	443(2)	
H-1-W-1	707(3)	857(2)	661(2)	
H-2-W-1	671(3)	861(2)	739(2)	
H-1-W-2	504(3)	599(2)	870(2)	
H-2-W-2	383(3)	616(2)	862(2)	
H-1-W-3	543(3)	854(3)	933(2)	
H-2-W-3	474(4)	779(2)	942(2)	

[a] E.s.d. values given in parentheses refer to the least significant digit. $B_{eq} = 4/3(\Sigma_{ij} B_{ij} a_i a_j)$, calculated from the refined anisotropic thermal parameters.

the carbon and oxygen atoms and positional parameters only for hydrogen atoms. The hydrogen atoms were given the isotropic equivalent temperature factors of the atoms to which they are bonded. The final cycle of refinement gave an R value of 0.031 for 1929 reflections and 319 parameters. The refinement data are included in Table I. Final atomic parameters and their estimated standard deviations are given in Table II. The atomic notation and thermal ellipsoids for the nonhydrogen atoms are shown in Fig. 1*.

Dehydration. — Lactulose·3 H_2O was dehydrated rapidly by heating samples at 57° in a vacuum oven. Samples removed at 1, 2, and 3 h had lost 79, 82, and 95% of the theoretical maximum amount of water of hydration. After treatment, the samples were stored in a vacuum dessicator prior to n.m.r. spectroscopic analysis.

Mutarotation. — Optical rotations, $[\alpha]_D^{20}$, were measured in a 10 cm cuvette using a Perkin–Elmer Model 141 polarimeter.

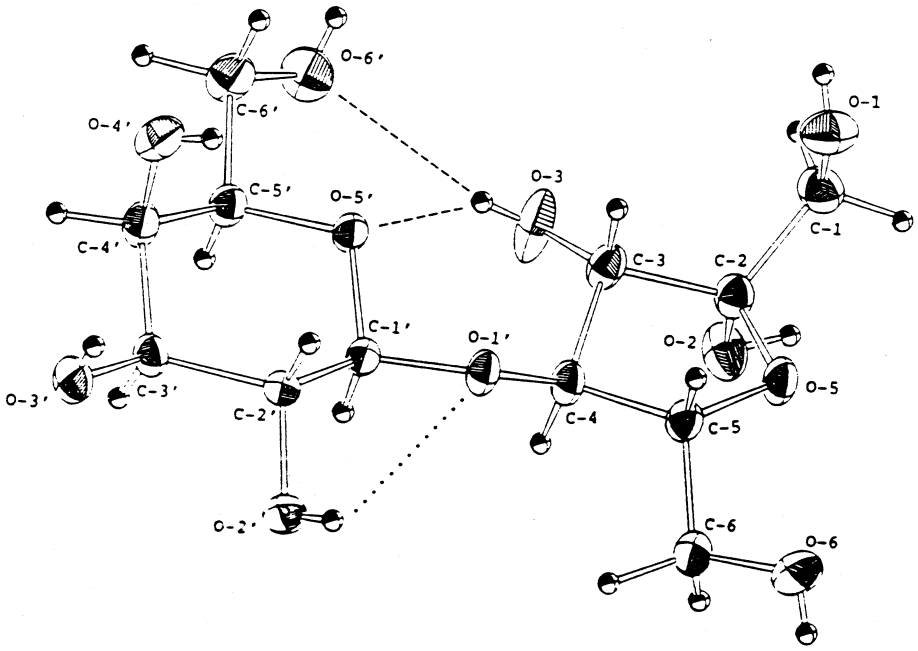


Fig. 1. Atomic notation and thermal ellipsoids (50% probability) for lactulose in the trihydrate crystal structure. The dashed lines are three-center, interresidue, intramolecular hydrogen bonds. The dotted line is the minor component of a four-center bond.

* Tables of anisotropic temperature factors and observed and calculated structure amplitudes have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P. O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/490/*Carbohydr. Res.*, 226 (1992) 29–42.

N.m.r. spectroscopy. — The ^{13}C CPMAS spectrum of the trihydrate, shown in Fig. 2a, has only two resolved resonances in the anomeric region (99 to 111 p.p.m.) corresponding to the anomeric C-2, at 105.3 p.p.m., and the protonated C-1′, at 102.9 p.p.m., of the β-fructofuranose isomer. The C-1′ resonance was identified by its suppression in the interrupted proton decoupled (IPD) spectrum[6] shown in Fig. 2b. This is in

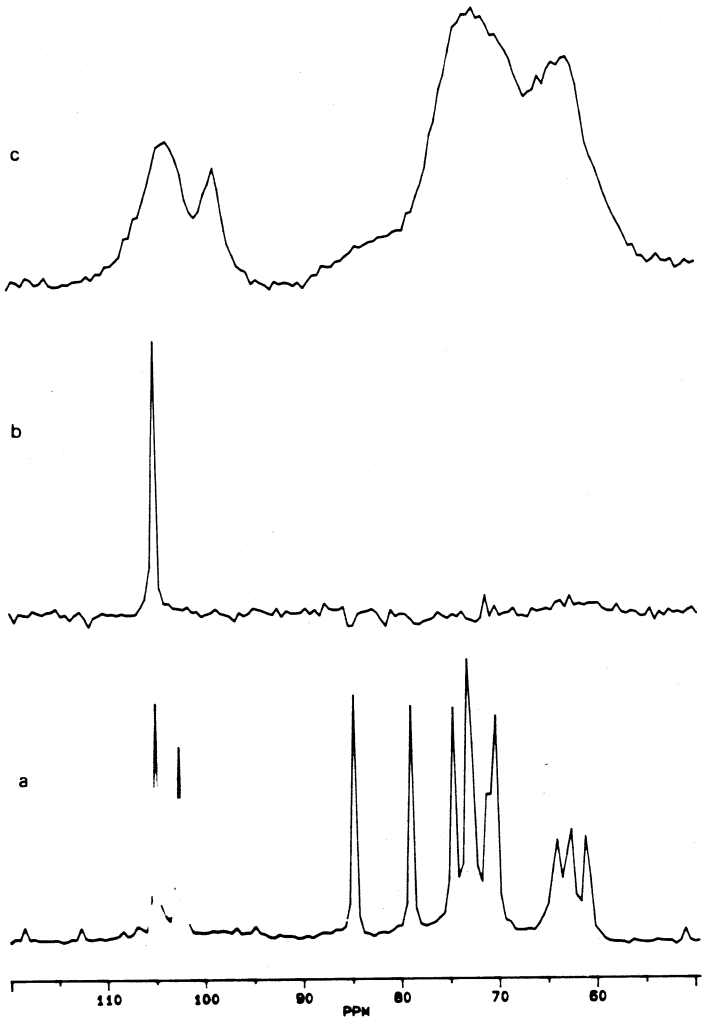


Fig.2 . ^{13}C CPMAS n.m.r. spectra of lactulose trihydrate. (a) 75.46 MHz Spectrum, 2000 scans, 2.5 s repetitions, 1.0 ms contact time, 12 G ^{1}H decoupling, 30 KHz spinning; (b) same as (a) except for the insertion of a 50 μs delay with no decoupling prior to acquisition (IPD conditions); (c) same as (a), for amorphous, dehydrated lactylose trihydrate.

contrast to the ^{13}C CPMAS spectrum of crystalline anhydrous lactulose, shown in Fig. 3b, which exhibited three C-2 resonances, at 99.6, 103.4, and 107 p.p.m., from the β-pyranose, β-furanose, and α-furanose isomers respectively[1], following suppression of the C-1′ resonances with IPD.

The C-2 resonance from the hydrate was identified as that of the β-furanose isomer by dissolving the hydrate in anhydrous dimethyl sulfoxide. As shown in Fig. 4, the freshly prepared solution showed only the protonated C-1′ resonance at 102.9 p.p.m., and the C-2 resonance at 103.4 p.p.m., matching the spectrum of the β-furanose component of the anhydrous lactulose[6]. On dehydration of the trihydrate, the amorphous powder gave the spectrum shown in Fig. 2c. This is a poorly resolved counterpart to the spectrum of the isomeric mixture found in crystalline anhydrous lactulose. Thus, it appears that the crystalline trihydrate converts into an isomeric mixture on dehydration in the solid state, as was verified by n.m.r. analysis. When dissolved in water lactulose trihydrate rapidly mutarotates, as shown in Table III, forming an equilibrium mixture of the α- and β-furanose and β-pyranose anomers. However, one could expect different behavior in dimethyl sulfoxide, since it is reported[7] that maltulose hydrate in this solvent showed no mutarotation over a period of 3 h. Indeed we found the mutarotation of lactulose trihydrate to be very slow in dimethyl sulfoxide, as shown by the n.m.r. data in Fig. 5. Therefore, the ^{13}C spectra of solutions in dimethyl sulfoxide

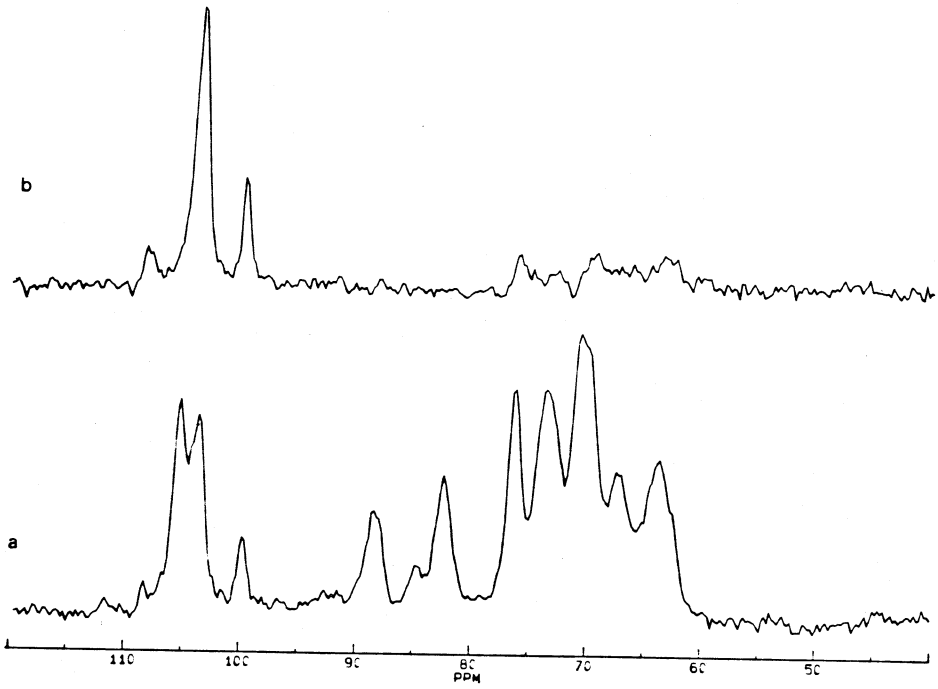


Fig. 3. Same as Fig. 2 except carried out with crystalline anhydrous lactulose. (a) Same as Fig. 2a; (b) same as Fig. 2b.

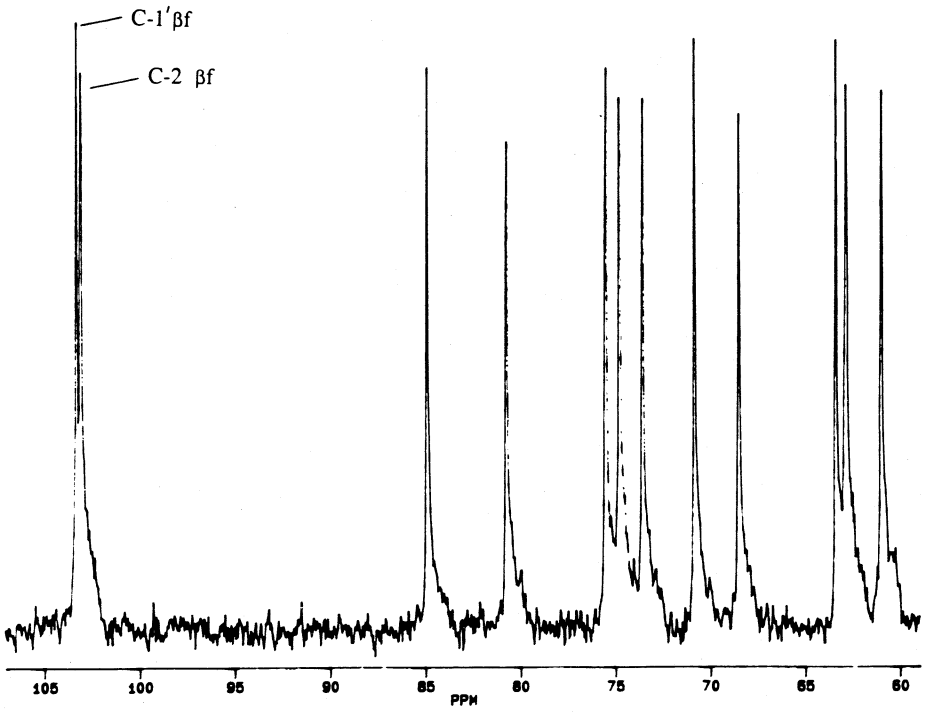


Fig. 4. 75.46 MHz ^{13}C spectrum of freshly dissolved lactulose trihydrate crystals in anhydrous Me_2SO. Assignments are as reported previously for this isomer as found in equilibrium with the α-furanose and β-pyranose forms[6].

TABLE III

Mutarotation of lactulose trihydrate[a]

Time (min)	*α obsd. (deg.)*	*Time (min)*	*α obsd. (deg.)*
3.08	−0.530	8.00	−1.355
3.43	−0.599	8.50	−1.418
3.70	−0.660	9.00	−1.479
4.00	−0.716	9.50	−1.536
4.50	−0.817	10.00	−1.591
5.00	−0.898	11.00	−1.695
5.37	−0.960	13.00	−1.858
5.85	−1.042	15.00	−1.995
6.50	−1.146	20.00	−2.216
7.00	−1.217		
7.50	−1.289	24 h	−2.520

[a] Determined in a 1 dm cell at 20°; c = 5.8182 g/100 mL, corresponding to 5.0248 g/100 mL of the anhydrous sugar. The rotation at 24 h corresponds to a specific rotation, $[\alpha]_D^{20}$, of −43.3° for the trihydrate, −50.2° for anhydrous lactulose.

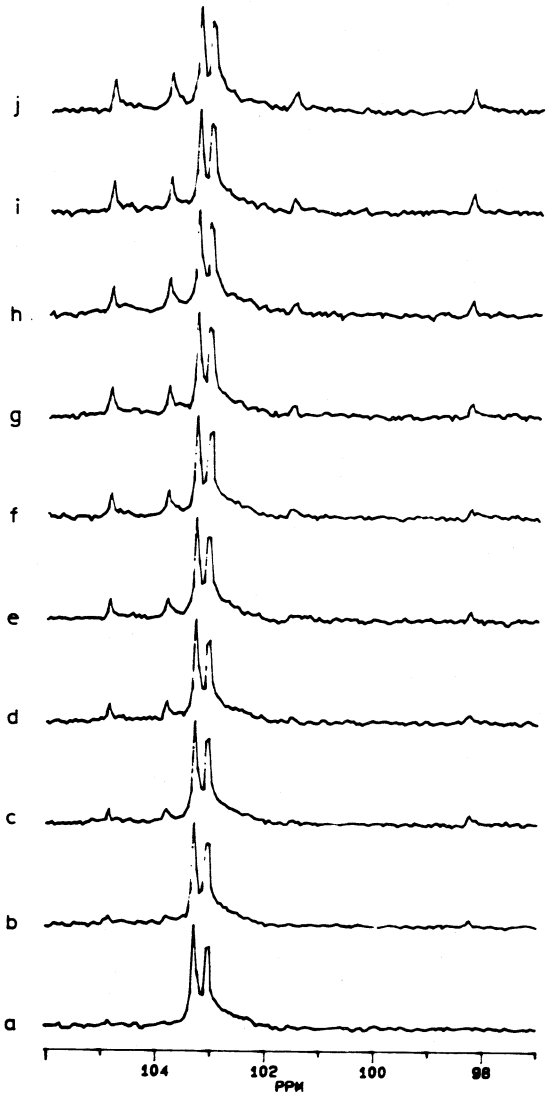


Fig. 5. 75.46 MHz ^{13}C spectra of the anomeric region of freshly dissolved lactulose trihydrate crystals in anhydrous Me_2SO. Spectrum (a) was taken 3 min after dissolution of the sugar; the successive further spectra were taken at 60 min intervals.

were used to determine the anomeric compositions of anhydrous lactulose, lactulose trihydrate, dehydrated amorphous lactulose, and water-equilibrated lactulose, giving the data summarized in Table IV.

Crystal structure analysis. — The results of the crystal structure analysis confirmed the sole presence of the β-fructofuranose isomer in the trihydrate. There is no evidence from the thermal parameters of isomeric or orientational disorder in the

TABLE IV

Anomeric composition of freshly dissolved lactulose in anhydrous Me_2SO as determined by n.m.r.

Sample	*Composition* (%)		
	β-Pyranose	*β-Furanose*	*α-Furanose*
Anhydrous lactulose	16.0	72.2	11.8
Lactulose trihydrate	–	100	–
Dehydrated lactulose trihydrate	37.5	40.8	21.7
Water equilibrated lactulose[a]	65.0	24.0	11.0

[a] A solution of anhydrous lactulose in water was allowed to mutarotate, then freeze-dried.

crystal structure. Therefore, this analysis provides more precise structural data for the lactulose molecule than that of the disordered anhydrous crystal structure previously reported[1]. The ring conformations in the molecule are as expected, with a pyranose $^4C_1$ chair and a $^4T_3$ (ψ = 272°) furanose ring. The overall conformation is stabilized by the intramolecular hydrogen bonds shown in Fig. 1. Selected torsion angles in the lactulose molecule are shown in Table V. The conformation of the molecule is very similar in the trihydrate and the anhydrous crystals, with a linkage-conformation angle O-5′–C-1′–O-1′–C-4 of − 79.9° in the trihydrate, compared with − 67° in the anhydrous structure. The C-1′–O-1′–C-4–C-3 angle in the trihydrate is 77.9°, compared with 84° in the anhydrous crystals.

The hydrogen bonding. — All hydroxyls, ring and glycosidic oxygen atoms, and water molecules are involved in the hydrogen bonding, which is completely ordered. The hydrogen bonding scheme is a three-dimensional network which can be decomposed into three infinite chains extending along the crystallographic axes, as shown in Fig. 6. In the *a* axis direction, the infinite chain consists of a sequence of six-membered *homodromic* cycles[8] shown in Fig. 7a. These are linked through W-3-H→W-2 bonds and extend through the operation of the two-fold screw axis. The infinite chain along the *c* axis is *antidromic*, having W-1 as double donor and O-6′ as double acceptor, shown in Fig. 7b. These two chains are linked through O-3′-H→O-6-H→W-2 and branch at W-2 and O-3′, which are double acceptors. The two-fold screw operations of the *a* and *c* chains along the *b* axis give rise to an infinite chain in the *b* direction, extending from W-2(2 565) to W-2(3 467). The individual hydrogen bond leng and angles, and the symmetry relations of the oxygen atoms, are given in Table VI, with the covalent O–H bond lengths normalized to 0.97 Å to correct for the bonding charge density[9]. The C–O–H angles range from 104.3 to 117.3° and the H–O–H angles from 100.0 to 110.8°. There is a three-centered interresidue intramolecular hydrogen bond, from O-3-H to O-5′ and O-6′, which is almost symmetrical. The three minor components of one three- and two four-center bonds are also intramolecular, *i.e.*, O-3′–H→O-4′-H→O-5′ and O-2′-H→O-1′.

TABLE V

Molecular geometry of lactulose in the crystalline trihydrate

Bond lengths (Å)			
C-1–C-2	1.512(4)	C-1–O-1	1.422(4)
C-2–C-3	1.537(4)	C-2–O-2	1.406(3)
C-3–C-4	1.520(4)	C-3–O-3	1.412(3)
C-4–C-5	1.510(4)	C-4–O-1′	1.428(3)
C-5–C-6	1.497(4)	C-5–O-5	1.446(3)
C-2–O-5	1.442(3)	C-6–O-6	1.423(4)
C-1′–C-2′	1.526(3)	C-1′–O-1′	1.389(3)
C-2′–C-3′	1.526(4)	C-2′–O-2′	1.420(3)
C-3′–C-4′	1.529(4)	C-3′–O-3′	1.429(3)
C-4′–C-5′	1.527(4)	C-4′–O-4′	1.420(3)
C-5′–C-6′	1.502(4)	C-5′–O-5′	1.440(3)
C-1′–O-5′	1.429(3)	C-6′–O-6′	1.432(4)
Bond angles (deg.)			
O-1–C-1–C-2	110.2(2)	O-1′–C-1′–C-2′	107.4(2)
C-1–C-2–C-3	114.6(2)	C-1′–C-2′–C-3′	109.8(2)
C-1–C-2–O-2	110.2(2)	C-1′–C-2′–O-2′	111.1(2)
C-1–C-2–O-5	108.5(2)	C-3′–C-2′–O-2′	107.9(2)
C-2–C-3–C-4	102.9(2)	C-2′–C-3′–C-4′	111.5(2)
C-2–C-3–O-3	110.2(2)	C-2′–C-3′–O-3′	111.0(2)
C-4–C-3–O-3	116.7(2)	C-4′–C-3′–O-3′	112.1(2)
C-3–C-4–C-5	101.1(2)	C-3′–C-4′–C-5′	108.6(2)
C-3–C-4–O-1′	116.6(2)	C-3′–C-4′–O-4′	113.4(2)
C-5–C-4–O-1′	106.5(2)	C-5′–C-4′–O-4′	112.2(2)
C-4–C-5–C-6	114.7(2)	C-4′–C-5′–C-6′	113.5(2)
C-4–C-5–O-5	105.8(2)	C-4′–C-5′–O-5′	109.4(2)
C-6–C-5–O-5	111.1(2)	C-6′–C-5′–O-5′	106.7(2)
C-5–C-6–O-6	108.5(2)	C-5′–C-6′–O-6′	107.6(2)
C-2–O-5–C-5	110.4(2)	C-1′–O-5′–C-5′	112.1(2)
Selected torsion angles (in deg.)			
Rings		*Others*	
C-2–C-3–C-4–C-5	39.12	O-1–C-1–C-2–O-5	− 60.5(3)
C-3–C-4–C-5–O-5	− 33.5(2)	C-1–C-2–O-5–C-5	132.9(2)
C-4–C-5–O-5–C-2	14.6(3)	C-2–O-5–C-5–C-6	139.8(2)
C-5–O-5–C-2–C-3	10.5(3)	O-5–C-5–C-6–O-6	69.5(3)
O-5–C-2–C-3–C-4	− 31.2(2)	O-1′–C-4–C-5–O-5	− 155.8(2)
C-1′–C-2′–C-3′–C-4′	− 52.4(3)	O-5′–C-5′–C-6′–O-6′	64.8(2)
C-2′–C-3′–C-4′–C-5′	53.5(3)	O-5′–C-1′–C-2′–O-2′	175.3(2)
C-3′–C-4′–C-5′–O-5′	− 58.1(3)	O-1′–C-1′–O-5′–C-5′	− 179.6(2)
C-4′–C-5′–O-5′–C-1′	64.8(3)	C-1′–O-5′–C-5′–C-6′	− 172.0(2)
C-5′–O-5′–C-1′–C-2′	− 63.2(2)		
O-5′–C-1′–C-2′–C-3′	55.6(3)		
Linkages			
O-5′–C-1′–O-1′–C-4	− 79.9(2)		
C-2′–C-1′–O-1′–C-4	162.2(2)		
C-1′–O-1′–C-4–C-5	− 170.3(2)		
C-1′–O-1′–C-4–C-3	77.9(3)		
C-1′–O-1′–C-4–H-4	− 50(1)		
H-1′–C-1′–O-1′–C-4	40(1)		

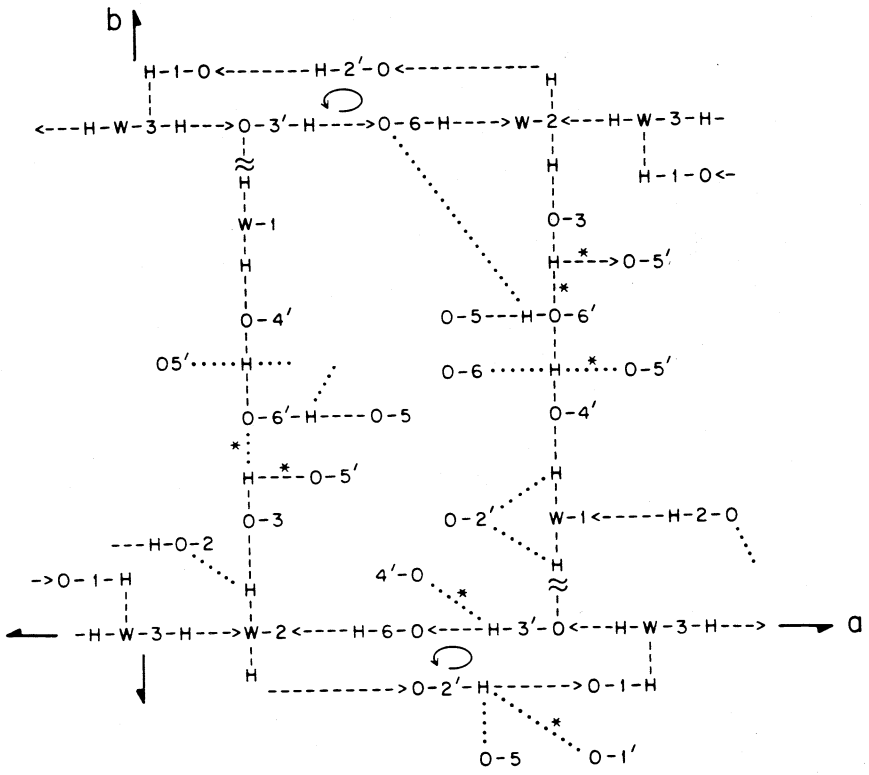


Fig. 6. The hydrogen-bonding scheme in the crystal structure of lactulose trihydrate. Dashed lines H - - - O ≤ 2.2 Å; dotted lines H ••• O > 2.2 Å; *intramolecular; homodromic cycle; ≈ to unit cell above.

bonds, and the other two form four-center bonds. All the hydroxyl and water oxygens are acceptors of strong hydrogen bonds, except the anomeric hydroxyl oxygen, O-2. Anomeric hydroxyls are commonly observed to be weak hydrogen-bond acceptors[9,10] Both the ring oxygens, O-5 and O-5', accept components of three-center hydrogen bonds, while the linkage oxygen, O-1', accepts an intramolecular minor component of a four-center bond. Of the three water molecules, W-1 and W-3 accept one hydrogen bond, while W-2 accepts two.

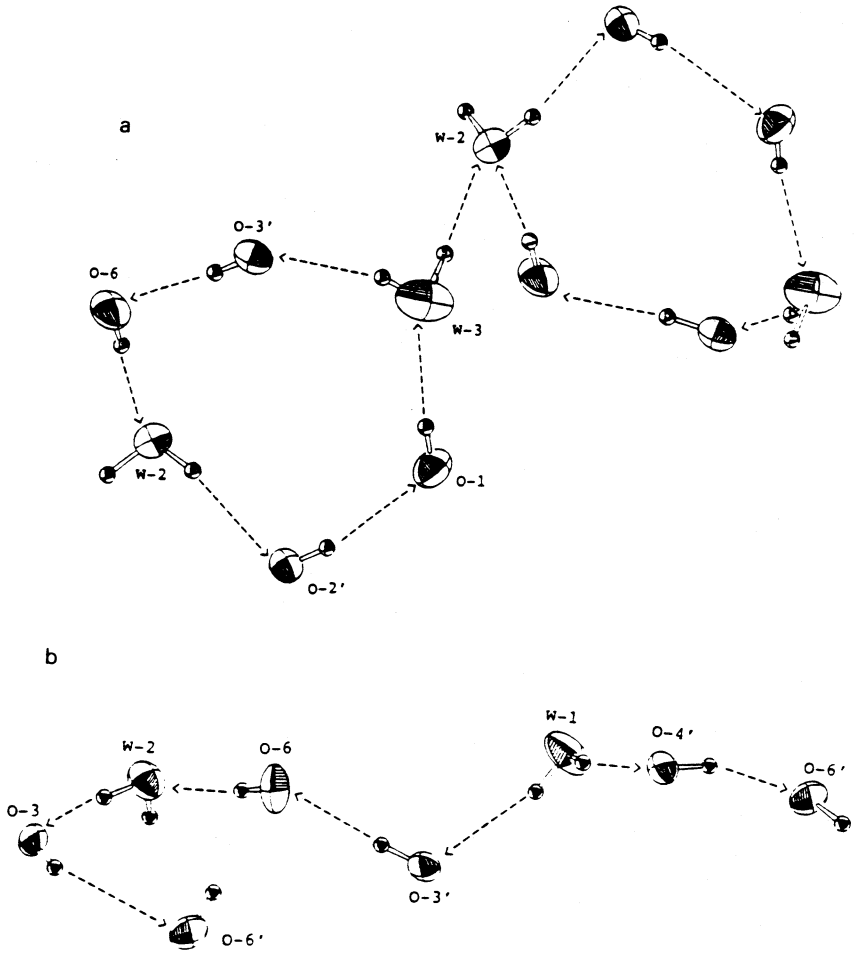


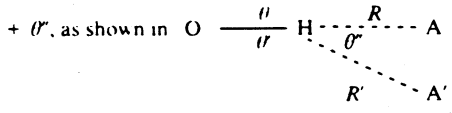
Fig. 7. Upper (a) the six-membered homodromic cycles extending along the *a* axis; lower (b), the antidromic chain along the *c* axis.

TABLE VI

The structural parameters of the hydrogen bonds in lactulose trihydrate[a]

Donor - - - - - acceptor	*Acceptor symmetry code*	R (Å)	Θ (deg.)	ΣΘ (deg.)[b]
Two-center bonds				
O-1-H - - - - - O-W-3	2 574	1.735	169.9	
O-2-H - - - - - O-W-1	4 656	1.838	166.7	
O-6-H - - - - - O-W-2	3 467	1.724	171.6	
Three-center bonds				
O-3-H - - - - - O-5′	1 555	2.116	136.9	359.3
O-6′	1 555	2.215	142.7	
O-3′-H - - - - - O-6	4 546	1.748	176.5	359.4
O 4′	1 555	2.624	95.5	
O-6′-H - - - - - O-5	2 574	2.081	157.2	354.3
O-6	2 574	2.367	115.6	
Four-center bonds				
O-1′	1 555	2.673	90.6	353.9
O-2′-H - - - - - O-1	4 546	1.789	163.4	
O-5	4 546	2.838	121.8	356.0
O-6	4 546	2.831	95.9	336.1
O-4′-H - - - - - O-6′	3 466	1.905	167.0	
O-5′	1 555	2.758	91.5	359.3
Water - - - - acceptors				
W-1-H-1 - - - - O-4′	3 566	2.072	164.3	359.9
O-2′	4 656	2.873	105.5	
W-1-H-2 - - - - O-3′	4 656	1.938	161.1	341.1
O-2′	4 656	2.818	110.0	
W-2-H-1 - - - - O-3	4 646	1.814	159.3	358.9
O-2	4 646	2.585	128.0	
W-2-H-2 - - - - O-2	1 555	1.761	167.0	
W-3-H-1 - - - - O 3	4 656	1.856	157.8	
W-3-H-2 - - - - O-W-2	1 555	1.825	167.4	

[a] O H bond lengths are normalized to 0.97 Å. Symmetry code: The three digits give the unit cell translation in the *a*, *b*, and *c* directions with respect to 555; the first digit of the symmetry code specifies one of the following operations: 1, *x*, *y*, *z*; 2, 1/2 − *x*, −*y*, 1/2 + *z*; 3, 1/2 + *x*, 1/2 − *y*, −*z*; 4, −*x*, 1/2 + *y*, 1/2 − *z*. [b] $\Sigma\theta = \theta + \theta' + \theta''$, as shown in



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REFERENCES

1 G. A. Jeffrey, R. A. Wood, P. E. Pfeffer, and K. B. Hicks, *J. Am. Chem. Soc.*, 105 (1983) 2128–2133.
2 G. A. Jeffrey, *Acta Crystallogr., Sect. B*, 42 (1990) 89–103.
3 P. E. Pfeffer, K. B. Hicks, and W. L. Earl, *Carbohydr. Res.*, 111 (1983) 181–194.
4 C. J. Gilmore, MITHRIL, *A Computer Program for the Automatic Solution of Crystal Structures from X-ray Data*, Department of Chemistry, University of Glasgow, Scotland, 1983.
5 J. O. Lundgren, *UPALS, A Full Matrix Least-Squares Refinement Program*, Institute of Chemistry, University of Uppsala, Sweden, 1978.
6 P. E. Pfeffer and K. B. Hicks, *Carbohydr. Res.*, 102 (1982) 11–22.
7 D. C. Craig, N. C. Stephenson, and J. D. Stevens, *Carbohydr. Res.*, 22 (1972) 494–495.
8 W. Saenger, *Nature (London)*, 279 (1979) 343–344.
9 G. A. Jeffrey and L. Lewis, *Carbohydr. Res.*, 60 (1978) 179–182.
10 T. C. Tse and M. D. Newton, *J. Am. Chem. Soc.*, 99 (1977) 611–613.